THERAPEUTIC OPTIONS FOR PRESERVATION OF RESIDUAL RENAL FUNCTION IN PATIENTS ON PERITONEAL DIALYSIS

Philip KamTao Li1 and Yuk Lun Cheng2

Department of Medicine and Therapeutics,1 Prince of Wales Hospital, Chinese University of Hong Kong, and Department of Medicine,2 Alice Ho Miu Ling Nethersole Hospital, Hong Kong SAR, PR China

Dialysis therapy remains the mainstay in the treatment of patients with end-stage renal disease. However, dialysis is not the ideal renal replacement therapy. It does not fully restore all the functions of failed kidneys, particularly the metabolic functions, with their complex feedback mechanisms.

Preservation of residual renal function (RRF), even in patients who have already been started on dialysis therapy, is of paramount importance. The presence of RRF is associated with better small and larger molecule clearances, better volume control, and better endocrine and metabolic functions. Hence, it is not surprising that a favorable effect of RRF on patient outcome has been noted (1–5).

Preservation of RRF has been observed to be better prolonged with peritoneal dialysis (PD) than with hemodialysis (HD). New dialysis patients treated with PD had a 65% lower risk of RRF loss than did those treated with HD (6). Once HD is started, RRF declines rapidly (7). The hypotheses that have been proposed to explain these findings include generation of inflammatory mediators by the HD circuit, the rapid intravascular contraction inherent in HD, and the lower pre-glomerular arterial pressure and lower protein intake among PD patients. Better-preserved RRF may contribute to the superior survival seen in PD patients as compared with HD patients in the first few years after initiation of dialysis therapy (8).

The foregoing findings all support the Hong Kong “PD first” policy—that is, to dialyze incident end-stage renal disease patients first with PD. Preservation of RRF is important in maintaining the longevity of PD treatment. In the present article, we discuss the impact of RRF on patient outcomes and the options available to preserve RRF in PD patients.

DISCUSSION

POTENTIAL IMPACT OF RRF

Residual renal function contributes substantially to the adequacy of PD. It helps to achieve solute removal targets and may obviate the need for additional PD exchanges. Preservation of 1 mL/min of residual glomerular filtration rate (GFR) has been found to spare as much as one 2-L dialysis exchange daily (9). A reduction in the number of PD exchanges minimizes disturbance to the social life of patients and theoretically reduces peritonitis secondary to contamination of the PD circuit during exchanges.

For patients with a bigger body build, the presence of RRF is particularly important in maintaining PD adequacy, because a higher urea distribution volume and surface area (and hence bigger denominators in the estimation of Kt/V and creatinine clearance) are expected. Assuming a dialysate-to-plasma creatinine ratio of 0.65,
each 1 mL/min of renal clearance can be translated into a weekly Kt/V of 0.25 – 0.3 and weekly creatinine clearance of 10 L, or a daily drainage volume of 2.2 L for a 70-kg male (10).

Finally, it should be noted that an increase in the exchange volume or frequency of PD cannot completely compensate for a decline in RRF. With regard to long-term outcome, 1 mL/min of RRF is believed to be more beneficial than is 1 mL/min of peritoneal creatinine clearance, given the more favorable impact of RRF.

Current guidelines for PD adequacy are based on the kinetics of small water-soluble molecules; they do not consider the role of other substances, such as larger molecules (11). Retention of those substances is thought to be related to some of the morbidity and mortality associated with chronic dialysis. For practical reasons (among others), these other molecules are not routinely monitored in dialysis patients, and practitioners should realize that clearances of those molecules depend mainly on RRF. Increasing the PD dose does not enhance the clearance of larger molecules (12).

Another objective of dialysis is to correct overhydration and to remove accumulated salt and water. Volume excess is an important cause of hypertension in dialysis patients, and hypertension is considered to be a major cause of morbidity and mortality. In this regard, our group showed that a lack of RRF is significantly associated with a higher left ventricular mass index in non-diabetic PD patients (13). Preserving RRF undoubtedly helps to maintain fluid balance and, hence, to control blood pressure and reduce the likelihood of left ventricular hypertrophy developing in dialysis patients.

Finally, the kidney is an important endocrine organ. It contributes to the activation of vitamin D and the production of erythropoietin. Unsurprisingly, calcium and phosphate balance is better in PD patients with RRF (5). Moreover, patients with better preserved RRF have been reported to be significantly less anemic and to require less erythropoietin treatment (13), probably because of higher levels of endogenous erythropoietin.

RRF AND OUTCOME

Increasing evidence supports a survival benefit for RRF preservation in PD patients (1–5). Prospective studies have demonstrated that residual GFR is an independent factor in patient survival (1,5). That finding is consistent with other studies that showed a lower mortality rate in non-anuric patients than in anuric PD patients (4,5). In this respect, Bargman et al. reanalyzed the CANUSA data and showed a 12% reduction in the risk for patient mortality for each 5 L/1.73 m² increment in weekly residual GFR and 36% for each 250-mL increment in daily urine volume in PD patients (2).

Another important facet in the proper management of end-stage renal disease patients is the provision of adequate nutrition. However, malnutrition is not uncommon in patients undergoing dialysis, and it is associated with significant morbidity and mortality (1,14). Estimates suggest that 8% – 10% and 30% – 35% of PD patients show evidence of severe or mild-to-moderate protein–energy malnutrition respectively (15). With regard to nutrition, our group has demonstrated a significant trend toward higher serum albumin levels in PD patients with better residual GFR (13). Moreover, we have also shown a significant and independent contribution of RRF to the actual dietary intakes of protein, calories, and other nutrients in PD patients (16). For each increment of 1 mL/min/1.73 m² in residual GFR, dietary calorie intake was noted to increase by a factor of 0.838, and dietary protein intake, by a factor of 0.041 (16).

Plasma C-reactive protein (CRP) is the prototypic marker of inflammation. Elevated levels of high-sensitivity CRP have been noted to be an independent risk factor for all-cause and cardiovascular mortality in PD patients, and a significant trend of increasing high-sensitivity CRP has been found with decreasing residual GFR in PD patients (3).

Vascular disease remains the leading cause of death in PD patients (1,3,4). It contributes to half the mortality in this population. Notably, as compared with PD patients with RRF, anuric PD patients have a higher overall mortality rate—a rate that has been almost completely attributed to the difference in mortality from vascular disease (4). Furthermore, patients without pre-existing cardiovascular disease at the initiation of PD more commonly died of vascular disease after they became anuric (4).

Thus, existing evidence suggests that a decline in RRF in PD patients is associated with more malnutrition, higher levels of inflammatory markers, and a higher prevalence of left ventricular hypertrophy and atherosclerotic complications—the “malnutrition, inflammation, atherosclerosis, calcification syndrome.” And in fact, an association between better quality of life and a higher residual GFR has recently been noted (17).

THERAPEUTIC OPTIONS TO PRESERVE RRF

Many studies in patients with chronic kidney disease have attempted to delineate the factors that accelerate a decline in renal function. Various renoprotective strategies have also been proposed (18). However, comparatively few relevant studies have been conducted in
patients on PD treatment. Based on currently available information, Table 1 lists possible therapeutic options for the preservation of RRF.

**Avoid Potentially Nephrotoxic Agents:** One approach to preserving RRF is to avoid (whenever possible) the use of nephrotoxic agents such as aminoglycosides and non-steroidal anti-inflammatories. Aminoglycosides are worth a larger discussion because they are commonly used in the treatment of PD-related peritonitis. In view of the potential nephrotoxic and ototoxic effect of aminoglycosides, the International Society for Peritoneal Dialysis guidelines published in 2005 recommend avoidance of extended or repeated courses of aminoglycoside therapy if an alternative approach is possible (19). However, short-term use of intraperitoneal aminoglycosides appears to be safe and to pose no harm to RRF (19,20). In this respect, a recent prospective randomized trial by Lui et al. suggested that PD-related peritonitis is associated with a significant but reversible reduction in RRF and daily urine volume at day 14 despite successful treatment of peritonitis. On the other hand, no difference was discerned with regard to the effect of a 2-week course of intraperitoneal netilmicin on RRF and urine volume in patients with PD and daily urine volume at day 14 despite successful treatment of peritonitis. On the other hand, no difference was discerned with regard to the effect of a 2-week course of intraperitoneal netilmicin on RRF and urine volume in PD patients with peritonitis (20).

**Judicious Use of Radiographic Dyes:** Contrast-media nephrotoxicity has been reported in the general population. Conventional high-osmolality contrast media are probably more nephrotoxic than are the newer low-osmolality contrast media. Other risk factors, such as older age, presence of diabetic nephropathy, volume depletion, cardiac failure, liver failure, and pre-existing renal insufficiency have also been reported (21). Because the proportion of elderly patients and the prevalence of diabetic nephropathy are increasing in the dialysis population, multiple risk factors for contrast-media nephrotoxicity are now more common in dialysis patients.

**TABLE 1**

<table>
<thead>
<tr>
<th>Therapeutic Options for Preservation of Residual Renal Function</th>
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<tbody>
<tr>
<td>1. Avoid nephrotoxic drugs (for example, aminoglycosides, non-steroidal anti-inflammatories)</td>
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<tr>
<td>2. Use radiocontrast dyes judiciously</td>
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<td>3. Optimize blood pressure control</td>
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<td>4. Avoid hypotension and dehydration</td>
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<td>5. Use angiotensin-converting enzyme inhibitors or angiotensin receptor blockers</td>
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<tr>
<td>6. Use biocompatible peritoneal dialysis solutiona</td>
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<td>7. Prevent peritoneal dialysis–related peritonitis</td>
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</table>

a Preliminary data.

A multifactorial pathogenesis of the condition is postulated, with a reduction in renal perfusion by direct effect of the agents and a resulting toxic effect on tubular cells now generally agreed to be the main factors (22). Reports concerning the general population are not lacking, but data on effect of contrast media on RRF in PD patients remain scarce.

Recently, two prospective studies reported a lack of any persistent effect of contrast media on RRF in continuous ambulatory peritoneal dialysis (CAPD) patients (23,24). One of these studies recruited 8 CAPD patients and showed a borderline significant difference in the time course of renal clearance, with the lowest level occurring on day 6 as compared with baseline (23). The effect on RRF was transient and was not observed on day 30. Moreover, no difference in RRF was noted between the study and the control groups. However, another prospective study by Moranne et al. noted no accelerated decline in RRF or daily urine volume on day 14 in 36 PD patients who were adequately hydrated before the contrast study and in whom a minimum volume (<200 mL) of iodinated contrast medium was used per radiologic investigation (24).

Based on these results, physicians should not refrain from contrast studies in the presence of a real clinical indication. However, the dose of the contrast medium must be as low as possible, and precautionary measures—for instance, adequate hydration—should be considered before the contrast study begins. Finally, practitioners should understand that no trial has yet been performed to test the usefulness of acetylcysteine in preserving RRF in PD patients; however, interest in using this drug to prevent contrast-media nephrotoxicity in patients with chronic kidney disease is increasing.

**Optimization of Blood Pressure Control:** In patients with chronic kidney disease, high blood pressure is well known to be negatively associated with renal function (18). Similar findings are observed in dialysis patients. A prospective observational study in incident dialysis patients by Jansen et al. found a negative effect of high diastolic blood pressure on RRF (7). Each 10-mmHg increase in diastolic blood pressure resulted in a 0.4 mL/min decrease in residual GFR (7). Noteworthy is the fact that declining RRF was also found to be independently associated with worsening blood pressure control (25). In other words, better-preserved RRF may lead to better blood pressure control, and optimized blood pressure control may better maintain RRF in PD patients.

Finally, control of dry body weight and multiple antihypertensive agents are usually required to achieve blood pressure goals in PD patients. However, dialyzing patients below their dry body weight is not desirable,
because dehydration in PD patients has been reported to be negatively associated with residual GFR (7).

Choice of Antihypertensive Agents: Many studies have suggested that certain antihypertensive agents offer additional renoprotection in patients with chronic kidney disease, and relevant guidelines have been proposed (18). For PD patients, the choice of antihypertensive agents may also help to preserve RRF. Use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or calcium channel blockers has been shown to be associated with decreased risk of RRF decline in PD patients (6,26,27). Our group performed the first prospective randomized study demonstrating the clinical benefit of ramipril, an ACE inhibitor, in PD patients (26). Our results suggest that ramipril significantly reduces the rate of RRF decline and that it also possibly delays the development of complete anuria in prevalent CAPD patients. After 12 months of ramipril, the relative odds of developing anuria in the ramipril treatment group as compared with the “no treatment” group was 0.578 (26).

Administration of ARBs is another approach to inhibiting the renin–angiotensin system. A prospective randomized trial by Suzuki et al. (27) demonstrated that RRF and daily urine volume were significantly better preserved by putting CAPD patients on an ARB (valsartan). Moreover, those authors also showed that the renoprotection persisted through the 2-year study period.

An increasing risk of loss of RRF over time among PD patients has been recognized (6,12). For new patients starting PD treatment (as contrasted with prevalent PD patients), administration of an ACE inhibitor or an ARB might better preserve RRF. As is the case in the non-dialysis population, the renoprotection of ACE inhibitors and ARBs appears to be independent of blood pressure control (26,27). Furthermore, both our group’s study and the one by Suzuki et al. showed that ramipril or valsartan was not effective in reducing proteinuria, and thus that an antiproteinuric effect was not the major mechanism for renoprotection (26,27).

Apart from their effect on the renin–angiotensin axis, ACE inhibitors may also suppress plasma levels of tumor necrosis factor alpha and CRP in chronic renal failure patients, which implies that other mechanisms may also be involved (28). Moreover, the use of ACE inhibitors has also been noted to be associated with a low prevalence of malnutrition (28). Although further study is required to confirm that finding, it and the potential renoprotection effect favor the use of ACE inhibitors or ARBs in PD patients (26–28).

In our study, no patients developed hyperkalemia that necessitated withdrawal of ramipril, partly because of the nature of continuous PD (26). Nevertheless, careful monitoring of serum potassium to detect hyperkalemia after initiation or increase in the dose of an ACE inhibitor or ARB is necessary, especially in patients with inadequate dialysis or low solute transport and in those who are noncompliant with dietary restrictions.

Use of Diuretics: Diuretics are generally useful for control of extracellular fluid volume expansion in dialysis patients with residual urine output. These agents may obviate the need for using a more hypertonic PD solution. Among the various classes of diuretics, loop diuretics are the most commonly used because they are effective in patients with advanced renal failure. In one study, long-term high-dose furosemide was found to be safe and to produce a significant increase in urine volume in PD patients (29). Although the drug was shown to have no effect on RRF preservation, it helped to maintain fluid balance in PD patients (29).

Choice of PD Solution: Conventional glucose-based PD solutions are not biocompatible. The low pH, high glucose content, and potentially cytotoxic glucose degradation products (GDPs) with subsequent development of advanced glycosylation end-products (AGEs) are believed to contribute to undesirable changes in the peritoneal membrane and its function.

Recently, new solutions with multi-compartment solution bags have been developed. A higher pH and reduced GDPs are advantages of these new solutions. Using one of low-GDP solutions in prevalent CAPD patients, Williams et al. (30) demonstrated that patients dialyzed for 12 weeks showed significant improvement in effluent markers of peritoneal membrane integrity and significantly decreased circulating AGE levels (30). Equally important, significantly higher RRF and daily urine volume were noted after patients were exposed to the 12-week trial of this PD solution (30). However, our group’s own randomized controlled trial of low-GDP solution did not show any significant difference in RRF (31).

Another, larger-scale prospective randomized controlled study, the balANZ study, is currently being performed to assess the effect on RRF preservation of low-GDP, neutral-pH PD solution. That study is anticipated to be completed in September 2010.

Other Possible Renoprotective Strategies: Considerable concern has been raised about the use of automated PD (APD) on the risk of RRF loss. Small studies of fewer than 20 APD patients have suggested that patients on APD experience a more rapid RRF loss than do patients on CAPD (32). The decline in RRF is hypothesized to be related to the rapid change in volume status and osmotic load in APD. However, in a large prospective observational study, APD was not observed to be associated with
a difference in RRF loss (6). Further prospective randomized trials are necessary to determine the significance of these findings. To minimize the use of more hypertonic PD solution in APD patients, measures such as fluid restriction and administration of diuretics may be considered.

The effect of PD peritonitis on RRF is the subject of some controversy. As previously mentioned, the randomized trial by Lui et al. suggests that peritonitis-related RRF loss is transient and reversible—regardless of the choice of antibiotics (20). However, data on the effect of refractory and repeated peritonitis on RRF is lacking. A retrospective study reported that peritonitis rate is associated with a more rapid decline of RRF (33). Given that peritonitis has also been reported to be the major cause of PD failure, measures to prevent PD peritonitis should be instituted for their possible renoprotective effect and to maintain the longevity of PD treatment.

Finally, negative effects of higher serum calcium (6) and proteinuria (7) on RRF have also been reported in large prospective observational studies. Regular monitoring of serum calcium is advisable, and measures to control proteinuria (for example, careful titration of ACE inhibitors or ARBs, or combination of these) may be considered. Additional randomized studies are needed to confirm those findings.

CONCLUSIONS

Preservation of RRF is very important in the proper management of dialysis patients. Residual renal function optimizes PD treatment and may obviate the need for additional PD exchanges, and hence may reduce the cost of PD treatment (9,10). It also improves outcomes, lowering mortality and morbidity, and is associated with a better quality of life. Interventions to correct the modifiable factors that can better maintain RRF should be considered. Moreover, it appears that patients may benefit most if renoprotective measures can be implemented early in PD treatment.

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REFERENCES


